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EXAMINER	
BALLARD, KIMBERLY	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,562	WEAVER ET AL.	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/03/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Claims **1-20** are pending and under examination in the current office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted January 3, 2007 has been considered and the references have been made of record.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, provisional Application No. 60/517,843 (filed 11/06/2003), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this

application. In the instant case, the '843 provisional application does not disclose the monoclonal antibodies secreted by the 226H or 236L hybridomas (i.e., mAbs 226H and 236L) that are instantly claimed. Support for these monoclonal antibodies is first noted in the PCT application US2004/037245 (filed 08/11/2004). Accordingly, for purposes of prior art, the effective filing date of instant claims 4-20 is **August 11, 2004**. Claims 1-3 are accorded benefit of the earlier priority date, November 6, 2003.

Claim Rejections - 35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 4-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods comprising the use of specific monoclonal antibodies secreted by hybridomas 217L, 226H and/or 236L, as well as specific amino acid sequences (CDRs) derived from these monoclonal antibodies.

The process of producing monoclonal antibodies is unpredictable; even when a small antigen is used multiple different monoclonal antibodies can be produced. See for example Kuby (Immunology, Third Edition, 1997, pp. 131-134), which teaches the

process by which monoclonals are produced. See also Alberts et al. (Molecular Biology of the Cell, Third Edition, 1994, pp. 1216 -1220). Alberts teaches the three-dimensional structure of antibodies is complex. Note particularly the large models on pp. 1219 - 1220 which indicate that the antibody molecules are comprised of hundreds of amino acids. The structure of a large protein such as an antibody is dependent not just on the antigen-binding region, but on the totality of the interactions of the hundreds of amino acid residues.

The specification fails to disclose the complete sequence and structure of monoclonal antibodies 217L, 226H or 236L, which are encompassed by the claims. The art recognizes that making monoclonals is an unpredictable process. Monoclonal antibodies are so unique that a skilled artisan cannot simply construct one, the actual hybridoma which secretes the antibody must be present in order to make it. Thus deposit of said hybridoma is required for compliance with § 112, first paragraph. MPEP § 2404.02 recognizes that when undue experimentation would be required for an artisan to make a biological product, deposit can be required. The examiner has concluded that in order to make the actual antibody F3D4, the hybridoma is required.

Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the enablement requirements of 35 USC §112, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.

The specification lacks sufficient deposit information for the monoclonal antibodies 217L, 226H, and 236L. Because these monoclonal antibodies are unknown, and therefore, publicly not available and cannot be reproducibly isolated from nature without undue experimentation, a suitable deposit for patent purposes is required. Note that the antibodies were first described by Gallatin et al. in US Patent 6,432,404 B1. The 217L, 226H, and 236L mAbs would not be expected to be reliably reproduced from any and all immunizations with the CD11d molecule.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be **irrevocably removed** upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

For the reasons above, it would not be possible for the skilled artisan to make and use the antibody recited in claims 4-10.

6. Claims 1-3 and 11-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating chronic pain resulting from spinal cord compression injury in a mammalian subject comprising administering to the subject in need a therapeutically effective amount of an antibody which specifically binds to CD11d, wherein the antibody comprises a light chain variable region comprising three complementarity determining regions (CDRs), or wherein the antibody comprises a heavy chain variable region comprising three CDRs, or wherein the

antibody comprises a full set of six CDRs, three from the heavy chain (VH) and three from the light chain (VL), does not reasonably provide enablement for a method of treating chronic pain associated with other conditions comprising administering any polypeptide or antibody fragment that specifically binds to CD11d. Furthermore, claims 19 and 20 are enabled for a method of treating chronic pain resulting from spinal cord injury in a mammalian subject comprising administering to the subject an antibody that specifically binds CD11d as specified above in conjunction with a pain relief medicine selected from the groups consisting of NSAIDs, analgesics, and anti-epileptic medicines, but are not enabled for the claimed methods as they read on treatment in conjunction with a steroid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant is advised that, if the biological deposit addressed in the previous rejection is perfected, claims 5-7 and 10 as they currently read would be included in the instant rejection.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are broadly drawn to a method of treating chronic pain in a mammalian subject comprising the step of administering to a subject in need a therapeutically effective amount of a composition comprising a polypeptide that specifically binds CD11d in conjunction with other pain relief medicine, wherein the other pain relief medicine is selected from the group consisting of NSAIDs, analgesics, steroids, and anti-epileptic medicines. Claims 5-7 and 10 are drawn to polypeptides or antibodies, comprising one, two and/or three CDRs of either a light chain (VL) or a heavy chain (VH) of a monoclonal antibody, or comprising one, two, three, four, five and/or six CDRs of a monoclonal antibody of hybridoma 217L, 226H or 236L. In other words, the binding polypeptide (antibody) recites alternative language such that less than the full set of CDRs (3 from each of the VH and the VL regions) are claimed.

There are three enablement issues pertinent to the instant rejection. Each will be discussed in turn.

First, regarding the patient population, the nature of the invention is the demonstration that administration of an anti-CD11d monoclonal antibody, 217L, to rats subjected to spinal cord compression injury at the T4 or T12 level leads to a significant reduction in symptoms of chronic pain (in this case tactile allodynia) as well as significant improvements in locomotor performance for several weeks following the injury (see Examples 1 and 2, pp. 29-34). The relevant art indicates that the treatment of chronic pain is highly complex and multifactorial, and although a variety of pharmacologic treatments have been and are currently available both at the time of filing and now, effective therapies for alleviating chronic pain are notably inadequate

(see reviews by Argoff CE. *J Am Osteopath Assoc.* 2002; Suppl 3, 102(9):S21-S26, and Katz WA et al. *Am J Therapeutics*, 2008; 15:256-264). Most notably, chronic pain can be the result of any number of medical conditions beyond spinal cord injury. For example, chronic pain can be associated with cancer and with non-cancer-related conditions such as migraine headaches, osteoarthritis, rheumatoid arthritis, postherpetic neuralgia, fibromyalgia, low back pain and other musculoskeletal conditions (see above reviews). However, the instant specification is limited to examples of neuropathic pain resulting from spinal cord compression injury, which is an art-accepted animal model of spinal cord injury. There is no evidence of record to indicate that the claimed therapeutic method would be at all effective in the treatment of, for example, cancer-related neuropathic pain or osteoarthritic chronic pain. As chronic pain is caused by different pathophysiologic processes, one of skill in the art could not reasonably predict that the CD11d integrin molecule is at all involved in the pathophysiology of any of these other conditions, such that inhibition of CD11d by a polypeptide/antibody that binds to CD11d would be capable of treating any chronic pain resulting from any condition, such as cancer or arthritis. The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution.

Second, regarding treatment with the claimed antibody in conjunction with a second agent, the present specification also clearly discloses that treatment with methylprednisone (an anti-inflammatory steroid) in combination with the CD11d antibody abolishes the positive neurological benefits of the anti-CD11d treatment (see

Example 5, pp. 37-38). These same findings are reiterated and expanded upon in a post-filing publication by the present Applicants (Weaver et al. *J Neurotrauma*, 2005; 22(12):1375-1387), again demonstrating that immunosuppressive therapy with methylprednisone negates the beneficial effects of anti-CD11d antibody treatment in spinal cord-injured rats, and noting that combination treatments causing intense immunosuppression should be viewed with caution (see abstract). Hence, both the instant disclosure and the relevant art recognize the unpredictability of therapeutic efficacy when combining an anti-CD11d antibody treatment with immunosuppressive agents such as steroids. It would not be expected, therefore, that the use of other steroids – which are all functionally immunosuppressive – would fare much differently from the effects of methylprednisone when used in conjunction with the claimed anti-CD11d antibody. Thus, one of skill in the art would require additional guidance in order practice the claimed method for treating chronic pain using a combinatorial treatment approach without resorting to undue experimentation.

Third, regarding the antibody being administered, the specification discloses only antibodies that contain both a VH and a VL chain with no less than 6 CDRs, 3 from the VH chain and 3 from the VL chain that bind to antigen, such as the monoclonal antibodies 217L, 226H and 236L. The specification also discloses polyclonal, single chain, chimeric, bifunctional/bispecific, humanized, human and CDR-grafted antibodies and binding fragments as well as peptibodies. However, in each of these instances a full set of 3 CDRs each for the light and heavy chains (or 6 CDRs total) would be necessary for specific binding to CD11d integrin. The specification does not enable

antibodies or polypeptides, or their non-binding fragments thereof, which do not contain the full set of 6 CDRs. Moreover, the broadest reasonable interpretation of claims 7 and 10 includes binding polypeptides having varying combinations of CDRs from the different disclosed monoclonal antibodies (217L, 226H, and 236L) within the heavy chain or the light chain (e.g., CDR1 from 217L, CDR2 from 226H, CDR3 from 236L, etc.) The specification does not enable combinations of different CDRs within a single VL or VH region wherein each CDR is derived from two or more different monoclonal antibodies, or different combinations of VL and VH domains from two different antibodies within a single specific binding region, to create a new monovalent antibody having uncharacterized binding function or specificity. The specification only provides guidance on various antibody species to the extent that within a given antigen binding site, both the VL and VH CDRs must be from the same parent monoclonal antibody.

It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, Third Edn. (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences

which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (*Proc Natl Acad Sci USA*, 1982; 79(6):1979-1983). The Rudikoff et al. reference teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibodies and fragments thereof as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing an antibody and polypeptide fragments thereof containing fewer than 6 CDRs, resulting in an antibody that retains the antigen specificity currently claimed. However, the claim language also reads on small amino acid sequences, which are incomplete regions of the variable region of the antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibodies as broadly as is claimed.

Due to the large quantity of experimentation necessary to determine whether treatment is effective in other types of chronic pain and whether other pain relief medicines would be effective in the combination treatment of chronic pain, the absence

of working examples directed to same, the complex nature of the invention, the unpredictably in the art with respect to treatment of chronic pain, the explicit evidence in the specification and the art indicating that use of immunosuppressive steroids is not only unpredictable but also ineffective, and the breath of the claims which includes the treatment of chronic pain resulting from any condition and the use of any pain relief medicine in conjunction with the claimed antibody (including notably ineffective combination therapies), undue experimentation would indeed be required to make and use the invention commensurate with the scope of the claims.

7. Claims 1, 5-9 and 11-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to methods of using a polypeptide that specifically binds CD11d and, in certain claims, comprises one to six CDRs of the light and/or heavy chains of specific monoclonal antibodies. The instant specification discloses "polypeptide" or "anti-CD11d...polypeptide" as those which "specifically bind to and recognize the CD11d molecule...including compounds that include one or more CDR sequences specifically recognizing the CD11d integrin." (see page 8, lines 22-29) Accordingly, the claims encompass use of a genus of polypeptide compounds related only by a desired function to specifically bind CD11d.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Applicants are directed to the recently-published guidelines on interpretation of the written description requirement, available on the internet at: http://www.uspto.gov/web/menu/written.pdf . In this case, the only factors present in the claims are a desired binding specificity of the claimed polypeptide molecules and, in limited claims, the inclusion of one or more CDRs derived from specific monoclonal antibodies. However, there is no explicit structural requirement for the polypeptides in most of the claims, and only limited structural requirements in a few claims (notably claims 5-7). The specification is open-ended with regard to the structure of such polypeptide compounds, as it encompasses peptide fragments having only one CDR sequence. While the structure/function relationship of specific antibody molecules is well known the art and provided in the instant specification in the form of such monoclonal antibodies as 217L, 226H and 236L, such is not the case for specifically binding polypeptides which can comprise structures entirely different and unique from traditional antibody species. Moreover, the specification does not indicate whether specific binding to the CD11d molecule alone is sufficient to provide therapy according to the claimed invention, or whether actual antagonism or inhibition of the CD11d molecule would also be required. Accordingly, in

the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of defined antibody molecules that specifically bind to the CD11d molecule, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods comprising the use of an antibody comprising a full set of CDRs, but not the full breadth of the claims meet the written description provision of

35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, second paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites the limitation "*the* spinal cord injury" [emphasis added] in lines 1-2 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 12-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Gris et al. (*J. Neuroscience*, 21 April 2004; 24(16):4043-4051; reference C26 on IDS filed 01/03/2007).

The claims are directed to a method for treating chronic pain in a mammalian subject comprising the step of administering to a subject in need a therapeutically effective amount of a composition comprising a polypeptide that specifically binds CD11d, wherein the chronic pain is selected from the group consisting of tactile allodynia, neuropathic pain, hyperalgesia, hyperpathia, and inflammatory paint (claim 12), wherein the pain is tactile allodynia (claim 13), the pain results from central nervous system trauma or spinal cord injury (claim 14) such as compression of the spinal cord (claim 15), wherein administration results in an increase in axon regeneration and/or growth (claim 16) or an increase in myelin regeneration (claim 17), and the composition further comprises a pharmaceutically acceptable diluent or carrier (claim 18).

Gris et al. report the successful use of an anti-CD11d monoclonal antibody (mAb) for reducing pain and improving neurological recovery following spinal cord injury in rats. The rats were subjected to spinal cord compression at levels T4 and T12 of the spinal cord column, producing models of autonomic dysreflexia and mechanical allodynia, respectively (see 1st column on page 4044), thus meeting limitations of claims 14 and 15. At 2, 24, and 48 hr following spinal cord injury (SCI), animals were intravenously administered saline (control), an isotype-matched irrelevant antibody, or the anti-CD11d mAb (see 1st column on page 4044). Because the control group is noted to have received normal saline, it would reasonably be expected that the antibodies would also be diluted in saline for i.v. administration to the animals, thus meeting a limitation of claim 18. Rats having received the anti-CD11d mAb were taught to exhibit improved locomotor activity scores and reduced mechanical allodynia (i.e.,

tactile allodynia), which is a measure of chronic pain (see Figures 1 and 2 on page 4045), thus addressing recited limitations of claims 12 and 13. Additionally, Gris et al. teach that anti-CD11d antibody treatment significantly enhanced myelin regeneration and neurofilament regrowth in the injured spinal cord (see, in particular, Figures 5-7), which would address limitations of claims 16 and 17. Accordingly, the teachings of Gris et al. clearly anticipate instant claims 12-18.

12. Claims 1-18 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 6,432,404 B1 to Gallatin et al. (issued August 13, 2002; reference A9 on IDS filed 01/03/2007).

The claims are directed to treatment of chronic pain in a mammalian subject comprising administration of a therapeutically effective amount of a composition comprising a polypeptide that specifically binds to CD11d, wherein the polypeptide is a monoclonal antibody such as 217L, 226H, 236L (claims 1-4), comprises light and/or heavy chain CDRs of these monoclonal antibodies (mAbs) (claims 5-7) and is a monoclonal, polyclonal, single chain, chimeric, bifunctiona/bispecific, humanized, human, or CDR-grafted antibody or a peptibody (claim 10), recognizes an epitope on CD11d recognized by these mAbs (claim 8), or competes with one of these mAbs (claim 9). Dependent claims further recite that the mammal is human (claim 11), types of chronic pain such as tactile allodynia (claims 12-13), pain resulting from CNS or spinal cord injury (SCI) such as compression of the spinal cord (claims 14-15), resultant increases in axon regeneration and/or growth (claim 16) or myelin regeneration (claim

17), and the composition further comprises a pharmaceutically acceptable diluent or carrier.

Gallatin et al. disclose a method for promoting locomotor recovery or inhibiting locomotor damage or limiting locomotor impairment following spinal cord injury by administering an effective amount of an anti-α_d monoclonal antibody to a spinal cord victim, wherein the administered monoclonal antibody is 217L or 226H (column 12, lines 47-56, and columns 97-99). Similarly, Gallatin et al. teach a method for reducing inflammation at the site of a central nervous system injury, such as spinal cord injury, comprising the step of administering to an individual an effective amount of an anti-α_d monoclonal antibody, wherein the antibody is the monoclonal antibody secreted by hybridoma 226H or by hybridoma 236L (column 11, lines 37-50). Exemplary spinal cord injuries treated by these methods are noted to include those involving compression to the spinal cord (column 12, lines 61-63), thus addressing limitations of instant claims 14 and 15. It is noted that the instantly recited CD11d integrin subunit is also called the α_d subunit of the $\alpha_d\beta_2$ heterodimeric integrin protein (aka CD11d/CD18) (see p. 1, lines 20-30 of the instant specification). Gallatin et al. also disclose the use of an anti-α_d monoclonal antibody that competes with 217L or 226H for binding to α_d (i.e., CD11d) (column 12, lines 56-58). Thus, Gallatin's disclosure addresses limitations recited in present claims 4-7 and 10 regarding a polypeptide comprising light or heavy chain CDRs from monoclonal antibodies 217L, 226H or 236L as well as limitations reciting that the claimed polypeptide would recognize an epitopes on CD11d recognized by 217L, 226H or 236L or compete with said mAbs, as in instant claims 8 and 9,

respectively. Gallatin et al. further disclose that the disclosed method also provides for the use of modified antibodies, such as single chain, chimeric. CDR-grafted, human and humanized antibodies (column 12, lines 1-10), thus meeting a limitation recited in instant claim 10.

In the treatment of spinal cord injury, antibodies were diluted in phosphate buffered saline, pH 7.2 (column 94, lines 34-36), thus addressing instant claim 18. While the treatment of a human subject is not explicitly recited by Gallatin et al., the treatment of human-specific conditions (e.g., Crohn's Disease), and noted statements that the clip compression injury (CCI) is a *clinically relevant* animal model of spinal cord injury (column 97, lines 17-19) provide evidence that, overall, the disclosed methods are clearly implied for use in the treatment of human patients, thus addressing instant claim 11. Further, because the same polypeptide (e.g., mAbs 217L, 226H or 236L) are administered in a therapeutically effective amount to the same patient population (e.g., victims of spinal cord injury, particularly compression of the spinal cord), the methods disclosed by Gallatin et al. would be expected to inherently treat the chronic pain associated with spinal cord injury (as in instant claims 12 and 13), as well as inherently result in axon regeneration and/or growth and increase myelin regeneration (as in instant claims 16 and 17). Evidence for such inherent results is presented at columns 97-98, wherein Gallatin teaches that rats subjected to CCI and treated with mAbs 217L, 226H or 236L exhibited clear increases in locomotor recovery compared to non-treated rats (column 98, lines 64-66), which is noted to be the same test applied in the instant

specification and correlated to axonal sprouting and reduced tactile allodynia. Thus, the teachings of Gallatin et al. anticipate the present invention of claims 1-18.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,432,404 B1 to Gallatin et al. (issued August 13, 2002; reference A9 on IDS filed 01/03/2007) in view of Eide (*Spinal Cord*, 1998; 36:601-612) and Argoff (*J. Am Osteopath Assoc*. September 2002; 102(9):S21-S26).

The teachings of Gallatin et al. are discussed above. Briefly, a method of treating spinal cord injury (SCI), which would include treatment of the chronic pain associated with SCI, comprising administering a composition comprising an effective amount of a monoclonal anti-CD11d antibody, such as 217L, 226H and 236L, are taught *inter alia* by Gallatin's disclosure. In an animal model of SCI, Gallatin demonstrates that administration of mAbs 217L, 226H and 236L significantly reduced the inflammatory response associated with SCI and effectively enhanced neurological recovery in the treated animals. However, Gallatin does not explicitly teach the use of other pain relief medicines used in conjunction with the antibody therapy.

Eide notes that after spinal cord injury, between 10% and 20% of patients develop central neuropathic (i.e., chronic) pain (see abstract). Moreover, Eide reports that in animal studies of SCI, chronic mechanical (tactile) allodynia appears in about 50% of the animals 1-6 weeks after injury and persists for several months (see 1st column on p. 606). Eide further comments that the study of chronic mechanical allodynia-like behavior in animals is most relevant for the clinical situation, and represents a useful animal model of central neuropathic pain (see 1st column on p. 606). Thus, one of ordinary skill in the art would clearly recognize that agents providing

therapy for SCI would also necessarily be efficacious for minimizing chronic pain associated with SCI.

Argoff teaches various pharmacologic therapies that have been used for the management of chronic pain, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioid and nonopioid analgesics, anticonvulsants (i.e., anti-epileptic drugs), antidepressants, α-adreneric agonists, muscle relaxants, topical agents, local anesthetics, NMDA receptor antagonists, and botulinum toxins (see, in particular, bottom of 1st column on page S23 and entire document in general). Argoff notes that healthcare providers must be aware of these available agents and how to use them rationally, either singly or in combination, so that patients with chronic pain can be treated as effectively as possible (see last paragraph in 2nd column on page S26).

It would have been obvious to one of ordinary skill in the art at the time the invention was filed to administer a pain-relieving agent as disclosed by Argoff in conjunction with the anti-CD11d monoclonal antibody disclosed by Gallatin for the treatment of chronic pain resulting from spinal cord injury. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to combining prior art elements according to known methods to yield predictable results. Moreover, the skilled artisan would be motivated to treat all neurological aspects of spinal cord injury in a human patient, which would encompass the treatment of chronic pain associated with the injury. Eide evidences that the animal model of spinal cord injury leading to mechanical allodynia is clinically relevant to the study of chronic pain. Such a model was utilized by Gallatin to

demonstrate the effectiveness of anti-CD11d monoclonal antibodies to treat spinal cord injury. Thus, the artisan would have a reasonable expectation that administration of an anti-CD11d monoclonal antibody in conjunction with a known pain-relieving medicine would result in the successful treatment of chronic pain resulting from spinal cord injury. Accordingly, the combined teachings of the above references render obvious the invention of claims 19 and 20.

Conclusion

15. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 9 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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